WEST

Create A Case

Select?	Database	Query	Plural	Op	Thesaurus	Set Name
☑	DWPI	1992WO-US07986!	YES	ADJ	ASSIGNEE	L1
☑	USPT	5648237	YES	ADJ	ASSIGNEE	L2
☑	USPT	5648237.pn.	YES	ADJ	ASSIGNEE	L3
☑	USPT	fas and gal4	YES	OR	ASSIGNEE	L4
☑	USPT	L4 and "death domain"	YES	OR	ASSIGNEE	L5
☑	USPT	L4 and "death domain" and "transmembrane domain"	YES	OR	ASSIGNEE	L6
☑	USPT	L4 and gal4 responsive	YES	ADJ		L7

Please enter the case name: 09446634

Clear All | Reset | Create Case | Cancel

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- Any other special characters or punctuation characters will be automatically removed prior to saving the case.
- All white space characters will be replaced by an underscore.

09/446,634

Your SELECT statement is:
s fas and pTK?

Items	File
10	5: Biosis Previews(R)_1969-2002/Aug W2
13	34: SciSearch(R) Cited Ref Sci_1990-2002/Aug W4
1	35: Dissertation Abs Online_1861-2002/Jul
7	71: ELSEVIER BIOBASE_1994-2002/Aug W3
11	73: EMBASE_1974-2002/Aug W3
1	94: JICST-EPlus_1985-2002/Jun W5
1	98: General Sci Abs/Full-Text_1984-2002/Jul
4	144: Pascal_1973-2002/Aug W4
1	149: TGG Health&Wellness DB(SM)_1976-2002/Aug W3
9	155: MEDLINE(R)_1966-2002/Aug W3
2	156: ToxFile_1965-2002/Aug W4
4	159: Cancerlit_1975-2002/Jul
2	266: FEDRIP_2002/Jun
2	370: Science_1996-1999/Jul W3
1	399: CA SEARCH(R)_1967-2002/UD=13708

SYSTEM:OS - DIALOG OneSearch
File 5:Biosis Previews(R) 1969-2002/Aug W2
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File 34:SciSearch(R) Cited Ref Sci 1990-2002/Aug W4
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File 73:EMBASE 1974-2002/Aug W3
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***File 73: Alert feature enhanced for multiple files, duplicates** removal, customized scheduling. See HELP ALERT.
File 155:MEDLINE(R) 1966-2002/Aug W3
***File 155: Alert feature enhanced for multiple files, duplicates** removal, customized scheduling. See HELP ALERT.
File 159:Cancerlit 1975-2002/Jul
(c) format only 2002 Dialog Corporation

Set	Items	Description
S1	47	FAS AND PTK?
S2	21	RD (unique items)
S3	8	S2 NOT PY=>1997

5/9/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

11920729 BIOSIS NO.: 199900166838
Activation-dependent transcriptional regulation of the human fas promoter requires NF-kappaB p50-p65 recruitment.
AUTHOR: Chan Henry; Bartos David P; Owen-Schaub Laurie B(a)
AUTHOR ADDRESS: (a)University Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Box 178, Houston, TX 770**USA
JOURNAL: Molecular and Cellular Biology 19 (3):p2098-2108 March, 1999
ISSN: 0270-7306
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: **Fas** (CD95) and **Fas** ligand (CD95L) are an interacting receptor-ligand pair required for immune homeostasis. Lymphocyte activation results in the upregulation of **Fas** expression and the acquisition of sensitivity to FasL-mediated apoptosis. Although **Fas** upregulation is central to the preservation of immunologic tolerance, little is known about the molecular machinery underlying this process. To investigate the events involved in activation-induced **Fas** upregulation, we have examined mRNA accumulation, **fas** promoter activity, and protein expression in the Jurkat T-cell line treated with phorbol myristate acetate and ionomycin (P/I), pharmacological mimics of T-cell receptor activation. Although resting Jurkat cells express **Fas** , **Fas** mRNA was

induced approximately 10-fold in 2 h upon P/I stimulation. Using sequential deletion mutants of the human **fas** promoter in transient transfection assays, we identified a 47-bp sequence (positions -306 to -260 relative to the ATG) required for activation-driven **fas** upregulation. Sequence analysis revealed the presence of a previously unrecognized composite binding site for both the Sp1 and NF-kappaB transcription factors at positions -295 to -286. Electrophoretic mobility shift assay (EMSA) and supershift analyses of this region documented constitutive binding of Sp1 in unactivated nuclear extracts and inducible binding of p50-p65 NF-kappaB heterodimers after P/I activation. Sp1 and NF-kappaB transcription factor binding was shown to be mutually exclusive by EMSA displacement studies with purified recombinant Sp1 and recombinant p50. The functional contribution of the kappaB-Sp1 composite site in P/I-inducible **fas** promoter activation was verified by using kappaB-Sp1 concatamers (-295 to -286) in a **thymidine kinase promoter** -driven reporter construct and native promoter constructs in Jurkat cells overexpressing IkappaB-alpha. Site-directed mutagenesis of the critical guanine nucleotides in the kappaB-Sp1 element documented the essential role of this site in activation-dependent **fas** promoter induction.

7/9/1 (Item 1 from file: 34)

03826776 Genuine Article#: QJ418 Number of References: 48

Title: YEAST TRANSCRIPTIONAL ACTIVATOR INO2 INTERACTS AS AN INO2P/INO4P BASIC HELIX-LOOP-HELIX HETEROMERIC COMPLEX WITH THE INOSITOL CHOLINE-RESPONSIVE ELEMENT NECESSARY FOR EXPRESSION OF PHOSPHOLIPID BIOSYNTHETIC GENES IN SACCHAROMYCES-CEREVISIAE

Author(s): SCHWANK S; EBBERT R; RAUTENSTRAUSS K; SCHWEIZER E; SCHULLER HJ
Corporate Source: UNIV ERLANGEN NURNBERG,INST MIKROBIOL BIOCHEM &GENET,LEHRSTUHL BIOCHEM,STAUDSTR 5/D-91058 ERLANGEN//GERMANY/; UNIV ERLANGEN NURNBERG,INST MIKROBIOL BIOCHEM &GENET,LEHRSTUHL BIOCHEM/D-91058 ERLANGEN//GERMANY/

Journal: NUCLEIC ACIDS RESEARCH, 1995, V23, N2 (JAN 25), P230-237
ISSN: 0305-1048
Language: ENGLISH Document Type: ARTICLE
Geographic Location: GERMANY
Subfile: SciSearch; CC LIFE--Current Contents, Life Sciences
Journal Subject Category: BIOCHEMISTRY & MOLECULAR BIOLOGY

Abstract: Coordinate transcriptional control of yeast genes involved in phospholipid biosynthesis is mediated by the inositol/choline-responsive element (ICRE) contained in the respective promoter regions. Regulatory genes INO2 and INO4, both encoding basic helix-loop-helix (bHLH) proteins, are necessary for ICRE-dependent gene activation. By the use of size variants and by heterologous expression in E.coli we demonstrate that Ino2p and Ino4p are both necessary and sufficient for the formation of the previously described **FAS** binding factor 1, Fbf1, interacting with the ICRE. Formation of a heteromeric complex between Ino2p and Ino4p by means of the respective bHLH domains was demonstrated in vivo by the interaction of appropriate two-hybrid constructs and in vitro by Far-Western analyses. Neither Ino2p nor Ino4p binds to the ICRE as a homodimer. When fused to the DNA-binding domain of GaI4p, Ino2p but not Ino4p was able to activate a UAS(**GAL**)-containing reporter gene even in the absence of the heterologous Fbf1 subunit. By deletion studies, two separate transcriptional activation domains were identified in the N-terminal part of Ino2p. Thus, the bHLH domains of Ino2p and Ino4p constitute the dimerization/DNA-binding module of Fbf1 mediating its interaction with the ICRE, while transcriptional activation is effected exclusively by Ino2p.

Set	Items	Description
S1	47	FAS AND PTK?
S2	21	RD (unique items)
S3	8	S2 NOT PY=>1997
S4	5	FAS AND THYMIDINE(W)KINASE(W)PROMOTER?
S5	1	RD (unique items)
S6	421	FAS AND GAL?
S7	1	S6 AND GAL4

09/446,634

Your SELECT statement is:
s fas and ppar

Items	File
23	5: Biosis Previews(R)_1969-2002/Aug W2
33	34: SciSearch(R) Cited Ref Sci_1990-2002/Aug W4
2	35: Dissertation Abs Online_1861-2002/Jul
11	71: ELSEVIER BIOBASE_1994-2002/Aug W3
15	73: EMBASE_1974-2002/Aug W3
2	98: General Sci Abs/Full-Text_1984-2002/Jul
7	144: Pascal_1973-2002/Aug W4
18	149: TGG Health&Wellness DB(SM)_1976-2002/Aug W3
20	155: MEDLINE(R)_1966-2002/Aug W3
4	156: ToxFile_1965-2002/Aug W4
5	159: Cancerlit_1975-2002/Jul
8	162: CAB HEALTH_1983-2002/Jul
1	266: FEDRIP_2002/Jun
1	370: Science_1996-1999/Jul W3
3	399: CA SEARCH(R)_1967-2002/UD=13708
1	444: New England Journal of Med._1985-2002/Aug W3

SYSTEM:OS - DIALOG OneSearch
File 5:Biosis Previews(R) 1969-2002/Aug W2
(c) 2002 BIOSIS
***File 5: Alert feature enhanced for multiple files, duplicates** removal, customized scheduling. See HELP ALERT.
File 34:SciSearch(R) Cited Ref Sci 1990-2002/Aug W4
(c) 2002 Inst for Sci Info
***File 34: Alert feature enhanced for multiple files, duplicates** removal, customized scheduling. See HELP ALERT.
File 155:MEDLINE(R) 1966-2002/Aug W3
***File 155: Alert feature enhanced for multiple files, duplicates** removal, customized scheduling. See HELP ALERT.
File 73:EMBASE 1974-2002/Aug W3
(c) 2002 Elsevier Science B.V.
***File 73: Alert feature enhanced for multiple files, duplicates** removal, customized scheduling. See HELP ALERT.

Set	Items	Description
S1	91	FAS AND PPAR
S2	43	RD (unique items)
S3	0	S2 AND GAL4
S4	4	S2 NOT PY=>1997 **6/9/1** **(Item 1 from file: 5)**

DIALOG(R)File 5:Biosis Previews(R)

12297835 BIOSIS NO.: 200000055702
Up-regulation of uncoupling protein 3 by thyroid hormone, peroxisome proliferator-activated receptor ligands and 9-cis retinoic acid in L6 myotubes.
AUTHOR: Nagase Itsuro; Yoshida Shigeru; Canas Xavier; Irie Yukiko; Kimura Kazuhiro; Yoshida Toshihide; Saito Masayuki(a)
AUTHOR ADDRESS: (a)Department of Biomedical Sciences, Laboratory of Biochemistry, Graduate School of Veterinary Medicine, Hokkaido University, Sapporo, 060-0818**Japan
JOURNAL: FEBS Letters 461 (3):p319-322 Nov. 19, 1999
ISSN: 0014-5793
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Uncoupling protein 3 (UCP3), expressed abundantly in the skeletal muscle, is one of the carrier proteins dissipating the transmitochondrial electrochemical gradient as heat, and thereby has been implicated in the regulation of energy metabolism. We have investigated UCP3 mRNA expression in the widely used L6 myocyte cell line by Northern blot analysis. UCP3 mRNA was not detected in L6 myoblasts, but appeared after their differentiation to myotubes. The UCP3 mRNA level was increased when L6 myotubes were treated with increasing concentrations of

triidothyronine (T3), oleic acid, alpha-bromopalmitate and **carbacyclin** , a non-selective ligand of peroxisome proliferator-activated receptors (PPARs), whereas it was not influenced when treated with selective ligands of PPARalpha (WY 14643) and PPARgamma (troglitazone). A ligand of retinoid X receptor (RXR), 9-cis retinoic acid, was also effective by itself and in combination with **carbacyclin** in stimulating UCP3 mRNA expression. The mRNA analysis of individual **PPAR** isoforms revealed that L6 cell expressed a significant level of PPARdelta but undetectable levels of PPARalpha and PPARgamma. These results suggest that UCP3 expression in myocytes is differentiation-dependent and regulated by the

6/9/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11165135 BIOSIS NO.: 199799786280
Up-regulation of UCP-2 gene expression by PPAR **agonists in preadipose and adipose cells.**
AUTHOR: Aubert Jerome; Champigny Odette; Saint-Marc Perla; Negrel Raymond; Collins Sheila; Ricquier Daniel; Ailhaud Gerard(a)
AUTHOR ADDRESS: (a)Centre de Biochimie, Universite de Nice-Sophia Antipolis, Faculte des Sciences, Parc Valrose, 06**France
JOURNAL: Biochemical and Biophysical Research Communications 238 (2):p 606-611 1997
ISSN: 0006-291X
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: UCP-2 is a member of the emerging family of UCP homologues. Upon high-fat feeding, UCP-2 mRNA levels are increased in epididymal fat pads of A/J mice, suggesting that the flux of fatty acids entering adipose tissue may regulate UCP-2 gene expression. Since fatty acids act as positive transcriptional regulators of lipid related genes by means of peroxisome proliferator-activated receptors (PPARs), the regulation of UCP-2 gene expression by **PPAR** agonists (**carbacyclin** , alpha-bromopalmitate, BRL49653) has been examined in mouse preadipose and adipose cells in primary cultures or from clonal lines (Ob1771, 3T3-F442A, 1B8). In preadipose cells, **carbacyclin** and a-bromopalmitate are active and BRL49653 shows no effect, whereas all these ligands are active in adipose cells. The stimulatory effect of **PPAR** agonists is potentiated by RXR agonists in adipose cells. In contrast to the UCP-1 gene, norepinephrine as a cAMP-elevating agent does not enhance the expression of UCP-2 gene. Altogether, the data favor a predominant role of **PPAR** -delta in preadipose cells and the involvement of **PPAR** -gamma-2 in adipose cells in upregulating UCP-2 gene expression. Thus, a potential link between fatty acid metabolism and thermogenesis may exist in **PPAR** -expressing tissues.

8/9/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11219717 BIOSIS NO.: 199800001049
Monoclonal antibodies as surrogate receptors in a high throughput screen compounds that enhance insulin sensitivity.
AUTHOR: Bright Stuart W(a); Gold Gerald; Sage Scott W; Sportman J Richard; Tinsley Frnak C; Dominianni Samuel J; Schmiegel Klaus K; Kellam Marcia L; Fitch Lora L; Yen Terence T
AUTHOR ADDRESS: (a)Lilly Corp. Cent., Eli Lilly and Co., Indianapolis, IN 46285**USA
JOURNAL: Life Sciences 61 (23):p2305-2315 Oct. 31, 1997
ISSN: 0024-3205
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Monoclonal antibodies (MoAbs) were made to a known insulin sensitivity enhancer (ISE) compound, **CS - 045** . The MoAbs were characterized with respect to binding other known thiazolidinedione ISE compounds using a **CS - 045** labeled with b-phycoerythrin in a

competitive particle concentration fluorescence immunoassay (PCFIA). By comparing the rank order of IC50 values for each compound to its respective potency as an ISE, one MoAb (13E3) was selected for further characterization. This MoAb was also used as a surrogate receptor in a high throughput screen to identify novel compounds that compete for binding to **CS - 045** . Some of the hits were found to have efficacy in reducing blood glucose. Subsequently, another group reported that several compounds with the core thiazolidinedione structure of the ISE compounds bound with high affinity to peroxisome proliferator-activating receptors (**PPAR**). Therefore, we used the MoAb assay to test these and other compounds that are known to bind to PPARgamma and noted crossreactivity with some of the compounds.

8/9/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10519016 BIOSIS NO.: 199699140161
Molecular cloning, expression and characterization of human peroxisome proliferator activated receptors gamma-1 and gamma-2.
AUTHOR: Elbrecht Alex(a); Chen Yuli; Cullinan Cathy A; Hayes Nancy; Leibowitz Mark D; Moller David E; Berger Joel
AUTHOR ADDRESS: (a)Dep. Molecular Endocrinol., Merck Res. Lab., P.O. Box 2000, Rahway, NJ 07065**USA
JOURNAL: Biochemical and Biophysical Research Communications 224 (2):p 431-437 1996
ISSN: 0006-291X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We describe the molecular cloning and expression of cDNAs encoding human **PPAR** -gamma-1 and **PPAR** -gamma-2. Our sequences are distinct from the published sequence at 3 positions, resulting in nonconservative amino acid substitutions. In humans, **PPAR** -gamma mRNA is expressed in spleen, bone marrow, liver, testis, skeletal muscle and brain, in addition to fat. Three thiazolidinediones were found to 1) displace a radiolabeled thiazolidinedione from both receptors with essentially the same IC-50s and 2) to transactivate both **PPAR** -gamma isoforms with similar EC-50s in transient cotransfection assays utilizing the adipocyte-specific aP2 promoter. Saturating concentrations of these 3 thiazolidinediones altered the conformation of in vitro synthesized **PPAR** -gamma protein producing a 27 kDa protease-resistant fragment. These results indicate that the antidiabetic effects of thiazolidinediones in humans are likely to be mediated via binding to and transactivation of **PPAR** -gamma-1 and gamma-2.

9/9/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13633388 BIOSIS NO.: 200200262209
PPAR activators as antiinflammatory mediators in human T lymphocytes: Implications for atherosclerosis and transplantation-associated arteriosclerosis.
AUTHOR: Marx Nikolaus(a); Kehrle Bettina; Kohlhammer Klaus; Grueb Miriam; Koenig Wolfgang; Hombach Vinzenz; Libby Peter; Plutzky Jorge
AUTHOR ADDRESS: (a)Department of Internal Medicine II, Cardiology, University of Ulm, Robert-Koch-Str. 8, D-89081, Ulm**Germany E-Mail: nikolaus.marx@medizin.uni-ulm.de
JOURNAL: Circulation Research 90 (6):p703-710 April 5, 2002
MEDIUM: print
ISSN: 0009-7330
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Activation of T lymphocytes and their ensuing elaboration of proinflammatory cytokines, such as interferon (IFN)-gamma, represent a critical step in atherogenesis and arteriosclerosis. IFNgamma pathways also appear integral to the development of transplantation-associated

arteriosclerosis (Tx-AA), limiting long-term cardiac allograft survival. Although disruption of these IFNgamma signaling pathways limits atherosclerosis and Tx-AA in animals, little is known about inhibitory regulation of proinflammatory cytokine production in humans. The present study investigated whether activators of peroxisome proliferator-activated receptor (**PPAR**)alpha and PPARgamma, with their known antiinflammatory effects, might regulate the expression of proinflammatory cytokines in human CD4-positive T cells. Isolated human CD4-positive T cells express PPARalpha and PPARgamma mRNA and protein. Activation of CD4-positive T cells by anti-CD3 monoclonal antibodies significantly increased IFNgamma protein secretion from 0 to 504+-168 pg/mL, as determined by ELISA. Pretreatment of cells with well-established PPARalpha (WY14643 or fenofibrate) or PPARgamma (BRL49653/rosiglitazone or pioglitazone) activators reduced anti-CD3-induced IFNgamma secretion in a concentration-dependent manner. **PPAR** activators also inhibited TNFalpha and interleukin-2 protein expression. In addition, **PPAR** activators markedly reduced cytokine mRNA expression in these cells. Such antiinflammatory actions were also evident in cell-cell interactions with medium conditioned by **PPAR** activator-treated T cells attenuating human monocyte CD64 expression and human endothelial cell major histocompatibility complex class II induction. Thus, activation of PPARalpha and PPARgamma in human CD4-positive T cells limits the expression of proinflammatory cytokines, such as IFNgamma, yielding potential therapeutic benefits in pathological processes, such as atherosclerosis and Tx-AA.

REGISTRY NUMBERS: 122320-73-4: **BRL / 49653** ; 122320-73-4: ROSIGLITAZONE; 50892-23-4: WY14643; 49562-28-9: FENOFIBRATE; 111025-46-8: PIOGLITAZONE
DESCRIPTORS:
MAJOR CONCEPTS: Blood and Lymphatics (Transport and Circulation); Immune System (Chemical Coordination and Homeostasis); Molecular Genetics (Biochemistry and Molecular Biophysics)
BIOSYSTEMATIC NAMES: Hominidae--Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGANISMS: human (Hominidae)
ORGANISMS: PARTS ETC: CD4-positive T cells--blood and lymphatics, immune system; T cells--blood and lymphatics, immune system; T lymphocytes--activation, blood and lymphatics, immune system
BIOSYSTEMATIC CLASSIFICATION (SUPER TAXA): Animals; Chordates; Humans; Mammals; Primates; Vertebrates
DISEASES: atherosclerosis--vascular disease; transplantation-associated arteriosclerosis--vascular disease
CHEMICALS & BIOCHEMICALS: **BRL / 49653** {rosiglitazone}--peroxisome proliferator-activated receptor gamma activator; CD64--expression; TNF-alpha {tumor necrosis factor-alpha}--expression; WY14643--peroxisome proliferator-activated receptor alpha activator; anti-CD3 monoclonal antibodies; fenofibrate--peroxisome proliferator-activated receptor alpha activator; interferon-gamma {IGN-gamma}--activation, pathways, secretion; interleukin-2 protein {IL-2 protein}--expression; major histocompatibility complex--induction; peroxisome proliferator-activated receptor alpha { **PPAR** -alpha}; peroxisome proliferator-activated receptor alpha mRNA { **PPAR** -alpha messenger RNA} ; peroxisome proliferator-activated receptor gamma { **PPAR** -gamma}; peroxisome proliferator-activated receptor gamma mRNA { **PPAR** -gamma messenger RNA}; peroxisome proliferator-activated receptor-alpha activator { **PPAR** -alpha activator}--antiinflammatory mediators; peroxisome proliferator-activated receptor-gamma activator { **PPAR** -gamma activator}--antiinflammatory mediators; pioglitazone--peroxisome proliferator-activated receptor gamma activator; proinflammatory cytokines--inhibitory regulation, production
MISCELLANEOUS TERMS: atherogenesis; cell-cell interactions; long-term cardiac allograft survival
ALTERNATE INDEXING: Atherosclerosis (MeSH)
CONCEPT CODES:
02506 Cytology and Cytochemistry-Animal
02508 Cytology and Cytochemistry-Human
03502 Genetics and Cytogenetics-General
03508 Genetics and Cytogenetics-Human
10064 Biochemical Studies-Proteins, Peptides and Amino Acids

14508 Cardiovascular System-Blood Vessel Pathology
15002 Blood, Blood-Forming Organs and Body Fluids-Blood and Lymph Studies
15004 Blood, Blood-Forming Organs and Body Fluids-Blood Cell Studies
17002 Endocrine System-General
34502 Immunology and Immunochemistry-General; Methods
BIOSYSTEMATIC CODES:
86215 Hominidae
?ds

Set	Items	Description
S1	91	FAS AND PPAR
S2	43	RD (unique items)
S3	0	S2 AND GAL4
S4	4	S2 NOT PY=>1997
S5	19	PPAR AND CARBACYCLIN
S6	13	RD (unique items)
S7	47	PPAR AND CS(W)045
S8	42	RD (unique items)
S9	235	PPAR AND BRL(W)49653

12/9/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11306729 BIOSIS NO.: 199800088061
Structural requirements and cell-type specificity for ligand activation of peroxisome proliferator-activated receptors.
AUTHOR: Johnson Timothy E(a); Holloway M Katharine; Vogel Robert; Rutledge Sue Jane; Perkins James J; Rodan Gideon A; Schmidt Ariel
AUTHOR ADDRESS: (a)Merck Res. Lab., WP45-305, West Point, PA 19486**USA
JOURNAL: Journal of Steroid Biochemistry and Molecular Biology 63 (1-3):p 1-8 Sept.-Oct., 1997
ISSN: 0960-0760
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The mammalian peroxisome proliferator-activated receptor (**PPAR**) family consists of three different subtypes, PPARalpha, hNUC1/PPARdelta and PPARgamma. Selective agonists have been identified for PPARalpha and PPARgamma but not for hNUC1, and consequently little is known about the genes that are controlled by this receptor. Using ligand-dependent transcription assays in COS-7 cells, we screened a variety of **PPAR** activating agents to identify a selective activator of hNUC1. We found that the potent peroxisome proliferator, Wy-14643, and the PPARgamma-selective thiazolidinedione, **BRL 49653** , were poor activators of hNUC1 (EC50s of >100 muM). Short chain fatty acids (**FAs**) appeared more selective for PPARalpha than for hNUC1, whereas the very long chain FA, erucic acid (C22:1) was more selective for hNUC1. Using erucic acid as a probe, we conducted a topological similarity search of the Merck Chemical Collection and identified a fatty acid-like compound, L-631,033 4-(2-acetyl-6-hydroxyundecyl) cinnamic acid, that was a selective activator of hNUC1 (EC50 of 2 muM), but was much less selective for PPARalpha or PPARgamma (EC50s of >100 muM). Structure-function analysis of **PPAR** activation by L-631,033 structural analogues showed that receptor selectivity depends on the position of the carboxyl group relative to the phenyl ring on the molecule. Transfection experiments in several cell types: an osteoblastic cell line (MB 1.8), a mouse liver cell line (ML-457), rat aortic smooth muscle cells (RSMCs) and COS-7 cells revealed differences in the activation profile of specific ligands. The most notable differences were observed in RSMCs, where transactivation by L-631,033 and Wy-14643, but not by **BRL 49653** , was markedly reduced, and in MB 1.8 cells, where oleic acid failed to activate PPARs. These findings identify certain structural features in **PPAR** -activating agents that modulate **PPAR** activation, and suggest that as with other nuclear receptors, activation is cell-type specific.

2/9/3 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

10372541 Genuine Article#: 517GL Number of References: 42

Title: Peroxisome proliferator-activated receptor gamma activators inhibit MMP-1 production in human synovial fibroblasts likely by reducing the binding of the activator protein 1

Author(s): Fahmi H; Pelletier JP; Di Battista JA; Cheung HS; Fernandes JC; Martel-Pelletier J (REPRINT)

Corporate Source: CHUM,Hop Notre Dame, Osteoarthritis Res Unit,1560 Rue Sherbooke Est,Y-2622 Pavillon Seve/Montreal/PQ H2L 4M1/Canada/ (REPRINT); CHUM,Hop Notre Dame, Osteoarthritis Res Unit,Montreal/PQ H2L 4M1/Canada/; Univ Miami,Sch Med, Dept Med,Miami//FL/33101

Journal: OSTEOARTHRITIS AND CARTILAGE, 2002, V10, N2 (FEB), P100-108

ISSN: 1063-4584 Publication date: 20020200

Publisher: W B SAUNDERS CO LTD, 24-28 OVAL RD, LONDON NW1 7DX, ENGLAND

Language: English Document Type: ARTICLE

Geographic Location: Canada; USA

Journal Subject Category: ORTHOPEDICS; RHEUMATOLOGY

Abstract: Objective: To investigate the expression and activity of PPARgamma in human synovial fibroblasts and the effects of PPARgamma agonists on the expression of MMP-1. The molecular mechanisms by which PPARgamma agonists modulate MMP-1 expression were also examined.

Methods: PPARgamma expression and activity were measured using reverse-transcription polymerase chain reaction (RT-PCR) and transient transfection assays. Human synovial fibroblasts were cultured with IL-1beta in the absence or presence of PPARgamma activators, and the expression and production of MMP-1 were evaluated by Northern blot and ELISA, respectively. The effect of 15d-PGJ(2) on MMP-1 promoter activation was analysed in transient transfection experiments, while electrophoretic mobility shift assays were performed to study the binding activity of the transcription factor AP-1.

Results: PPARgamma was expressed and transcriptionally functional in human synovial fibroblasts. PPARgamma activators (15d-PGJ(2) and **BRL 49653**) inhibited IL-1beta-induced MMP-1 synthesis in a dose-dependent manner. Similarly, both activators inhibited IL-1-induced MMP-1 mRNA expression. Activation of the human MMP-1 promoter was also attenuated by 15d-PGJ(2), indicating that the inhibitory effect of 15d-PGJ(2) occurs at the transcriptional level. Interestingly, 15d-PGJ(2) reduced both basal and IL-1beta-induced AP-1 binding activity.

Conclusions: These data indicate that PPARgamma agonists inhibit MMP-1 gene expression by transcriptional mechanisms, and suggest that they may be useful in reducing joint tissue destruction. (C) 2002 OsteoArthritis Research Society International.

Descriptors--Author Keywords: **PPAR** gamma ; MMP-1 ; synovial fibroblasts ; AP-1

Identifiers--KeyWord Plus(R): **FAS** -MEDIATED APOPTOSIS; **PPAR** -GAMMA; 15-DEOXY-DELTA(12,14)-PROSTAGLANDIN J(2); RHEUMATOID-ARTHRITIS; COLLAGENASE GENE; ADIPOCYTE DIFFERENTIATION; EXPRESSION; OSTEOARTHRITIS; INTERLEUKIN-1-BETA; METALLOPROTEINASES

09/446,634

3/9/1
DIALOG(R)File 155:MEDLINE(R)

13487921 21585479 PMID: 11728217
Anticytokine therapy for osteoarthritis.
Goldring M B
Division of Rheumatology, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA 02115-5713, USA. mgoldrin@bidmc.harvard.edu
Expert Opin Biol Ther (England) Sep 2001, 1 (5) p817-29, ISSN 1471-2598 Journal Code: 101125414
Contract/Grant No.: R01-AR45378; AR; NIAMS
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Subfile: INDEX MEDICUS
Osteoarthritis (OA) is a joint disease that involves degeneration of articular cartilage, weakening of the subchondral bone and limited intra-articular inflammation manifested by synovitis. Since the pathogenesis of OA involves multiple aetiologies, including mechanical, biochemical and genetic factors, it has been **difficult** to identify unique targets for therapy. Current pharmacological interventions focus primarily on improving symptoms. The rationale for the use of anticytokine therapy in OA is based on evidence from studies in vitro and in vivo that interleukin-1 (IL-1) and tumour necrosis factor (TNF)-alpha are the predominant pro-inflammatory and catabolic cytokines involved in the initiation and progression of articular cartilage destruction. Since the increased levels of catabolic enzymes, prostaglandins, nitric oxide (NO) and other markers in OA fluids and tissues appear to be related to elevated levels of IL-1 and TNF-alpha, therapies that interfere with the expression or actions of these cytokines are most promising. Other cytokines that are anti-inflammatory and are often detected, paradoxically, in OA tissues are also potential therapeutic agents for counteracting the cartilage destruction in OA. Identification of methods for early diagnosis is of key importance, since therapeutic interventions aimed at blocking or reversing structural damage will be more effective when there is the possibility of preserving normal homeostasis. At later stages, cartilage tissue engineering with or without **gene therapy** will also require anticytokine therapy to block damage to newly repaired cartilage. This review will focus on experimental approaches currently under study that may lead to elucidation of effective strategies for therapy in OA, with special emphasis on anticytokine therapy. (113 Refs.)

4/9/3
DIALOG(R)File 155:MEDLINE(R)

13400667 22068061 PMID: 12072533
PG13 packaging cells produce recombinant retroviruses carrying a diphtheria toxin mutant which kills cancer **cells.**
Qiao Jian; Caruso Manuel
Le Centre de Recherche en Cancerologie de l'Universite Laval, L'Hotel Dieu de Quebec, Centre Hospitalier Universitaire de Quebec, Quebec G1R 2J6, Canada.
Journal of virology (United States) Jul 2002, 76 (14) p7343-8, ISSN 0022-538X Journal Code: 0113724
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Subfile: INDEX MEDICUS
The development of suicide **gene therapy** with gene products that are directly toxic to cells, such as the A subunit of diphtheria toxin (DT-A), has been hampered by the **difficulty** of engineering recombinant viruses. DT-A is a strong inhibitor of protein synthesis that acts by ADP-ribosylating elongation factor 2, and a low level of DT-A expression in virus producer cells prevents the production of recombinant virus. We analyzed here the natural resistance of packaging cells to DT-A toxicity, and we report that PG13 and PA317 packaging cell lines are resistant to H21G, a DT-A mutant. PG13 cells produce recombinant H21G virus that efficiently kills a variety of human **tumor** cells. Our finding indicates

that PG13 packaging cells provide a new potential for the development of DT-A-based suicide **gene therapy** .

5/9/1

DIALOG(R)File 155:MEDLINE(R)

13123215 21894167 PMID: 11899081

Gene therapy **for diabetes mellitus.**

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Curr Mol Med (Netherlands) Jul 2001, 1 (3) p325-37, ISSN 1566-5240 Journal Code: 101093076

Document type: Journal Article; Review; Review, Academic

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Subfile: INDEX MEDICUS

There are diverse strategies for **gene therapy** of diabetes mellitus. Prevention of beta-cell **autoimmunity** is a specific **gene therapy** for prevention of type 1 (insulin-dependent) diabetes in a preclinical stage, whereas improvement in insulin sensitivity of peripheral tissues is a specific **gene therapy** for type 2 (non-insulin-dependent) diabetes. Suppression of beta-cell apoptosis, recovery from insulin deficiency, and relief of diabetic complications are common therapeutic approaches to both types of diabetes. Several approaches to insulin replacement by **gene therapy** are currently employed: 1) stimulation of beta-cell growth, 2) induction of beta-cell differentiation and regeneration, 3) genetic engineering of non-beta cells to produce insulin, and 4) transplantation of engineered islets or beta cells. In type 1 diabetes, the therapeutic effect of beta-cell proliferation and regeneration is limited as long as the **autoimmune** destruction of beta cells continues. Therefore, the utilization of engineered non-beta cells free from **autoimmunity** and islet transplantation with immunological barriers are considered potential therapies for type 1 diabetes. Proliferation of the patients' own beta cells and differentiation of the patients' own non-beta cells to beta cells are desirable strategies for **gene therapy** of type 2 diabetes because immunological problems can be circumvented. At present, however, these strategies are technically **difficult** , and transplantation of engineered beta cells or islets with immunological barriers is also a potential **gene therapy** for type 2 diabetes. (113 Refs.)

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DIALOG(R)File 155:MEDLINE(R)

10691683 20236877 PMID: 10777119

New treatment possibilities in rheumatoid arthritis.

Forre O; Haugen M; Hassfeld W G

Center for Rheumatic Diseases, The National Hospital, Oslo, Norway. o.t.forre@klinmed.uio.no

Scandinavian journal of rheumatology (NORWAY) 2000, 29 (2) p73-84, ISSN 0300-9742 Journal Code: 0321213

Document type: Journal Article; Review; Review, Academic

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Subfile: INDEX MEDICUS

It is very **difficult** to predict future treatment modalities especially in diseases like rheumatoid arthritis (RA) with unknown etiology and pathogenesis. In the near future, traditional disease-modifying antirheumatic drugs (DMARD) alone, in combination with each other, or together with cyclosporine, FK506, Rapamycin, or Leflunomide, will probably be the main treatment for RA. Currently biological anti-TNFalpha agents like humanized MAb and recombinant TNF-receptor constructs are now launched in the market. This therapy alone, or in combination with methotrexate is very effective in RA patients. There are, however, concerns over increase in serious infections. Autologous stem cell transplantation will probably be used in certain patient with serious **autoimmune** diseases. (113 Refs.)

5/9/3

DIALOG(R)File 155:MEDLINE(R)

09993323 98435426 PMID: 9762678

A gene therapy approach to treat demyelinating diseases using non-replicative herpetic vectors engineered to produce cytokines.

Martino G; Furlan R; Galbiati F; Poliani P L; Bergami A; Grimaldi L M; Adorini L; Comi G

Exp. Neuroimmunotherapy Unit-DIBIT, San Raffaele Scientific Institute, Milano, Italy.

Multiple sclerosis (Houndmills, Basingstoke, England) (ENGLAND) Jun 1998, 4 (3) p222-7, ISSN 1352-4585 Journal Code: 9509185

Document type: Journal Article; Review; Review, Tutorial

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Subfile: INDEX MEDICUS

A successful **gene therapy** approach in organ-specific **autoimmune** diseases, such as multiple sclerosis (MS), encompasses the inhibition of the autoreactive T cells or the modification of the target organ cells by the introduction of exogenous 'protective' genes. In MS, an **autoimmune** disease of the central nervous system (CNS), the inciting autoantigen is still unknown and therefore the isolation of autoreactive T cells may only be inferential. At present, **gene therapy** approaches in MS should therefore aim to the modification of the target organ. Possible candidate genes to be transferred within the CNS of MS patients are those coding for anti-inflammatory cytokines (i.e. interleukin-4, interleukin-10, transforming growth factor beta) which have been shown to ameliorate demyelinating diseases at least in experimental models. However, a limiting factor for this therapy is the **difficulty** to reach the CNS. A **gene therapy** approach using viral vectors able to infect post-mitotic cells, such as those present within the CNS, without inducing toxic reactions, may overcome this limitation. We propose to use non-replicative herpetic vectors, which represent a viable gene-transfer alternative to the classical retroviral and adenoviral vectors. Key advantages are their size, able to accommodate multiple foreign genes, and their ability to infect post-mitotic cells such as those present within the CNS. We first transferred a gene coding for interleukin-4 within the CNS of mice undergoing experimental allergic encephalomyelitis, an animal model for MS, using non-replicative Herpes Simplex Virus type 1-derived vectors. We found that this approach ameliorates the disease course and delays the disease onset. The establishment of this technique to deliver anti-inflammatory cytokines within the CNS using herpetic vectors should clarify the role of individual cytokines in the demyelinating process and allow assessment of whether **gene therapy** using herpetic vectors is a feasible and safe approach to treat human demyelinating disorders. (37 Refs.)

Set	Items	Description
S1	18741	GENE(W)THERAPY
S2	821	S1 AND FAIL?
S3	422	S1 AND DIFFICULT?
S4	129	S3 AND (CANCER OR TUMOR OR NEOPLASM)
S5	6	S3 AND AUTOIMMUN?